

10-20-00

PTO/SB/05 (4/98)

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	8308
First Inventor or Application Identifier	Paul John Rennie
Title	Compositions For Prevention and Treatment of Cold and Influenza-Like Symptoms and Their Methods of Use
Express Mail Label No.	EJ302199429US

APPLICATION ELEMENTS

See MPEP Chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

1. ☒ * Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original, and a duplicate for fee processing)
2. ☒ Specification Total Pages ☐
(preferred arrangement set forth below)
 - Descriptive Title of the Invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R&D
 - Reference to Microfiche Appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. ☐ Drawing(s) (35 USC 113) Total Sheets ☐
4. Oath or Declaration Total pages ☐
 - a. ☒ Newly executed (original or copy) **UNSIGNED**
 - b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 16 completed)
 - i. ☐ **DELETION OF INVENTORS**
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR §§1.63(d)(2) and 1.33(b).

5. ☐ Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
 - a. ☐ Computer Readable copy
 - b. ☐ Paper Copy (identical to computer copy)
 - c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment Papers (cover sheet & document(s))
8. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)
9. ☐ English Translation Document (if applicable)
10. ☐ Information Disclosure ☐ Copies of IDS
Statement (IDS)/PTO-1449 Citations
11. ☐ Preliminary Amendment
12. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
13. ☐ *Small Entity ☐ Statement filed in prior application
Statement(s) Status still proper and desired
14. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
15. ☐ Other:

NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37. C.F.R. §1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. §1.28).

16. If a **CONTINUING APPLICATION**, check appropriate box and supply the requisite information below and in the preliminary amendment:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. 1

Prior application information: Examiner: _____ Group/Art Unit: _____

For **CONTINUATION** or **DIVISIONAL** only: The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

☐ Customer Number or Bar Code Label

(Insert Customer No. or Attach bar code label here)

or ☐ Correspondence address below

NAME	John M. Howell				
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	8700 Mason-Montgomery Road				
CITY	Mason	STATE	Ohio	ZIP CODE	45040
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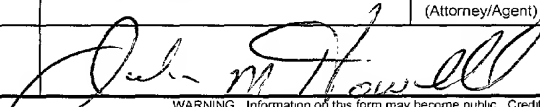
Name (Print/Type)	John M. Howell	Registration No. (Attorney/Agent)	33,713
Signature	<i>John M. Howell</i>	Date	October 19, 2000

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Box Patent Application, Washington, D.C. 20231.

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FEE TRANSMITTAL for FY 2001 Patent fees are subject to annual revision	Complete if Known	
	Application Number	
	Filing Date	October , 2000
	First Named Inventor	Paul John Rennie
	Examiner Name	
	Group/Art Unit	
TOTAL AMOUNT OF PAYMENT (\$)	1304.00	Attorney Docket No., 8308

METHOD OF PAYMENT (check one)		FEE CALCULATION (continued)																																																																																																																																																																																											
1. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge indicated fees and credit any over payments to: Deposit Account Number 16-2480 Deposit Account Name The Procter & Gamble Company <input checked="" type="checkbox"/> Charge Any Additional Fee <input type="checkbox"/> Applicant claims small entity status. See 37 CFR §127 Required Under 37 C.F.R. §§1.16 and 1.17		3. ADDITIONAL FEES <table border="1"> <thead> <tr> <th>Large Fee Code</th> <th>Entity Fee (\$)</th> <th>Small Fee Code</th> <th>Entity Fee (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>105</td><td>130</td><td>205</td><td>65</td><td>Surcharge - late filing fee or oath</td><td><input type="checkbox"/></td></tr> <tr><td>127</td><td>50</td><td>227</td><td>25</td><td>Surcharge - late provisional filing fee or cover sheet</td><td><input type="checkbox"/></td></tr> <tr><td>139</td><td>130</td><td>139</td><td>130</td><td>Non-English specification</td><td><input type="checkbox"/></td></tr> <tr><td>147</td><td>2,520</td><td>147</td><td>2,520</td><td>For filing a request for <i>ex parte</i> reexamination</td><td><input type="checkbox"/></td></tr> <tr><td>112</td><td>920*</td><td>112</td><td>920*</td><td>Requesting publication of SIR prior to Examiner's action</td><td><input type="checkbox"/></td></tr> <tr><td>113</td><td>1,840*</td><td>113</td><td>1,840*</td><td>Requesting publication of SIR after Examiner's action</td><td><input type="checkbox"/></td></tr> <tr><td>115</td><td>110</td><td>215</td><td>55</td><td>Extension for reply within 1st month</td><td><input type="checkbox"/></td></tr> <tr><td>116</td><td>390</td><td>216</td><td>195</td><td>Extension for reply within 2nd month</td><td><input type="checkbox"/></td></tr> <tr><td>117</td><td>890</td><td>217</td><td>445</td><td>Extension for reply within 3rd month</td><td><input type="checkbox"/></td></tr> <tr><td>118</td><td>1,390</td><td>218</td><td>695</td><td>Extension for reply within 4th month</td><td><input type="checkbox"/></td></tr> <tr><td>128</td><td>1,890</td><td>228</td><td>945</td><td>Extension for reply within 5th month</td><td><input type="checkbox"/></td></tr> <tr><td>119</td><td>310</td><td>219</td><td>155</td><td>Notice of Appeal</td><td><input type="checkbox"/></td></tr> <tr><td>120</td><td>310</td><td>220</td><td>155</td><td>Filing a brief in support of an appeal</td><td><input type="checkbox"/></td></tr> <tr><td>121</td><td>270</td><td>221</td><td>135</td><td>Request for oral hearing</td><td><input type="checkbox"/></td></tr> <tr><td>138</td><td>1,510</td><td>138</td><td>1,510</td><td>Petition to institute a public use proceeding</td><td><input type="checkbox"/></td></tr> <tr><td>140</td><td>110</td><td>240</td><td>55</td><td>Petition to revive - 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SUBMITTED BY		Complete (if applicable)	
Name (Print/Type)	John M. Howell	Registration No. (Attorney/Agent)	33,713
Signature		Telephone	(513) 622-2184
		Date	October 19, 2000

WARNING: Information on this form may become public. Credit Card information should not be included on this form. Provide credit card information and authorization on PTO-2038

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COMPOSITIONS FOR PREVENTION AND TREATMENT
OF COLD AND INFLUENZA-LIKE SYMPTOMS
AND THEIR METHODS OF USE

5 Paul John Rennie
Simon Phillip King
Kimberly Ann Biedermann
Jeffery Michael Morgan

10 CROSS REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of prior applications Serial Nos. 09/421,131 (P&G Case 7831), filed on October 19, 1999; the application is incorporated herein by reference.

FIELD OF USE

15 The present invention is for compositions and their methods for prevention and treatment of cold and influenza-like symptoms due to respiratory tract viral infections. These compounds and their method of application are effective in both preventing the onset of the symptoms of colds and influenza or significantly mitigating them if already afflicted with such symptoms.

BACKGROUND SUMMARY OF THE ART

20 It is known that many different viruses and viral strains bring on symptoms associated with respiratory viral infections. The common cold is a complex syndrome caused by over 200 antigenically different viruses found in five virus families. These families include rhinovirus, myxovirus, paramyxovirus, respiratory syncytial virus, adenovirus and coronavirus. The most important group is rhinovirus, Gwaltney J.M., Common Cold, pp 489-493, Mandell G.L., Douglas, R.G. Jr., Bennett, J.E., Principles and Practice of Infectious Diseases, 3rd ed., Churchill
25 Livingstone, New York, 1990. Pinpointing the specific cause of the illness is difficult and not practical since there are also a number of predisposing factors whose contribution to the manifestation of symptoms is not fully understood. Such include, but, are not limited to physical fatigue, psychological stress, and overall physical healthiness.

30 Regardless of the virus and associated factors leading to the onset of cold and influenza symptoms, a number of remedies to alleviate the symptoms of the common cold have been suggested. The cough/cold products that are currently marketed typically contain one or more of the following actives: nasal decongestants such as pseudoephedrine, oxymetazoline, antihistamines such as doxylamine, antitussives such as dextromethorphan, expectorants such as guaifenesin and anti-pyretics such as acetaminophen. In an attempt to improve existing cold

remedies, experts in the field have suggested several alternative pharmacotherapies and subsequently conducted cold trials to test their efficacy. Examples of these therapies include: the use of interferon- α_2 , Douglas et al., Prophylactic Efficacy of Intranasal Alpha₂- Interferon Against Rhinovirus Infection in the Family Setting, The New England Journal of Medicine, 314, pp. 65-70, 1986; bradykinin antagonist, Higgins et al., A Study of the Efficacy of the Bradykinin Antagonist, NPC567, in Rhinovirus Infections in Human Volunteers, Antiviral Research vol. 14, pp. 339-344, 1990; glucocorticoid, Farr et al., A Randomized Controlled Trial of Glucocorticoid Prophylaxis Against Experimental Rhinovirus Infection, Journal of Infectious Diseases, vol. 162, pp. 1173-1177, 1990; nedocromil, Barrow et al., The Effect of Intranasal Nedocromil Sodium on Viral Upper Respiratory Tract Infections in Human Volunteers, Clinical and Experimental Allergy, vol. 20, pp. 45-51, 1990; a combination of interferon- α_2 , ipratropium and naproxen, Gwaltney, Combined Antiviral and Antimediator Treatment of Rhinovirus Colds, The Journal of Infectious Diseases vol. 166, pp. 776-782, 1992; zinc salts, Potter et al., DIAS Rounds, Zinc Lozenges for Treatment of Common Colds, The Annals of Pharmacotherapy, vol. 27, pp. 589-592, 1993.

A number of patents have also been issued disclosing compositions for prevention and treatment of the common cold and their methods of use. A sample of such patents include: US Patents 5,240,694; 5,422,097; and 5,492,689; all to Gwaltney, disclosing treatment using combinations of anti-viral and anti-inflammatory compounds; US Patents Re 33,465 and 5,409,905; both to Eby disclosing treatment using zinc salts; US Pat. 5,626,831; to Van Moerkerken disclosing treatments using orally administered aminocarboxylic acid compounds; U.S. Patents 4,619,934 and 4,552,899, both to Sunshine, disclosing treatment of cough and colds using compositions comprising non-steroidal anti-inflammatory drugs such as NSAIDS with antihistaminically effective materials such as chlorpheniramine.

Treatment for influenza includes vaccination and use of specific antiviral drugs. These have been reviewed by A. Elliot and J. Ellis, 2000, Pharmaceutical Journal, 265, 446-451. Amantidine and Rimantidine have been used for treating influenza infections. They target the M2 protein of influenza virus and interfere with release of viral genetic material into the infected cell, thus preventing viral replication. A number of side effects have been reported including neurological and gastro-intestinal complaints, Belshe, R.B., Smith, M.H., Hall, CB, Betts, Hay, R.J., Genetic basis of Resistance to Rimantidine Merging During Treatment of Influenza Virus Infection, Journ. of Virology, 1988, 62, 1508-12; Hay, A.J., The Action of Adamantanamines Against Influenza A Viruses: Inhibition of the M2 Ion Channel, Protein. Semin Virol., 1992, 3, 21-30.

Another approach to influenza treatment has been to inhibit the neuraminidase enzyme molecule on the virus, important to the virus' replication and infectivity. One such treatment drug is Zanamivir, developed by Glaxo Wellcome, Monto, A.S., Robinson, D.P., Herlocher, M.L., Hinson, J.M., Elliot, M.J., Crisp, A., Zanamivir in the prevention of influenza among healthy adults: A randomized controlled trial. JAMA, 1999, 282, 31-5. Side effects reported were sinusitis, diarrhea, nausea and adverse lung effects. A second neuraminidase inhibiting drug is Oseltamivir, licensed under the trade name Tamiflu, Treanor, J.J., Hayden, F.G., Vrooman, P.S., Bararush, R. Bettis, R., Riff, D. Efficacy and safety of the oral neuraminidase inhibitor Oseltamivir in treating acute influenza: A randomized controlled study. JAMA, 2000, 283, 1016-24. There is a concern with Amantidine, Rimantidine and Neuraminidase inhibitors that viral resistance may develop, rendering them ineffective. A. Elliot and J. Ellis, 2000, Pharmaceutical Journal, 265, 446-451.

US Patent 4,689,223, issued August 25, 1987, assigned to T&R Chemicals, discloses compositions for treating the symptoms of or preventing the common cold nasal sprays comprising sulphites or bisulphites having low, but, not a specific pH disclosed. EP046409, published February 24, 1982, to Walliczek, discloses processes for preparation of solution of cuprous complexes for therapeutic treatment of human or animal body; incorporated herein by reference. The process discloses preparation of cuprous complex with ascorbic acid or non toxic ascorbate having a pH from 4-6. The complex may be used to make solutions for topically treating fungal, inflammatory or viral complaints. US Patent 6,080,783, issued June 27, 2000, assigned to Gum Tech International, Inc., herein incorporated by reference, discloses viscous gels for delivering minor effective homeopathic amount of zinc or another metal to the nasal membrane. The compositions maintain ionic zinc in direct contact with the nasal membrane and delivers rapidly zinc into the nasal membrane and into blood in those membranes for treating colds.

A known characteristic of rhinoviruses is that they lose infectivity under acidic conditions. Even pH values of 5.0 are known to reduce Rhinovirus infectivity, Hughes, J.H., Acid Lability of Rhinovirus Type 14: Effect of pH, Time and Temperature, Proc. Soc. Exp. Biol. Med., 1993, 144, 555-60. EP310317, published April 5, 1989 to Bordt et al., assigned to Beecham, discloses a method for inactivating viruses and bacteria with pharmaceutical compositions including vaccines prepared by inactivating viruses or bacteria with ascorbic acid or its salts in presence of oxygen and heavy metal ions. US Patents 4,767,788, Diana, issued August 30, 1988, assigned to Sterling Drug Inc., discloses processes for destroying viruses with glutaric acid including rhinovirus in the nasal mucosa.

Despite the abundance of compositions and preventative treatments known in the art, there remains a need to provide a consistent and effective method for prevention and treatment of cold and influenza symptoms.

SUMMARY OF THE INVENTION

5 The present invention is for respiratory tract compositions and methods for using such compositions for prevention and treatment of cold and influenza-like symptoms due to respiratory tract viral infections. The compositions of the present invention comprise pyroglutamic acid and an organic acid having a pKa value from about 3.0 to about 5.0, wherein the combination of said pyroglutamic and organic acids provides a surface pH of the nasal cavity
10 tissue from about pH 3.5 to 5.5. Upon application to the nasal tissues, the compositions create an environment hostile to viruses. Such an environment deters viruses from infecting the host wherein the host exhibits the symptoms mentioned above. The present invention also includes treating already infected subjects in order to mitigate the above-mentioned cold and flu symptoms. Also claimed as part of the invention are the methods of reducing or eliminating the
15 possibility of acquisition of such viruses when confronted with a high-risk public environment including schools and office buildings.

DEFINITIONS

The following are the definitions that should be applied to the terms used to describe the present invention:

20 “Respiratory tract compositions” refers to compositions in a form that is directly deliverable to the airway passages from the nose and mouth. These compositions include, but are not limited to droppers, pump sprayers, pressurized sprayers, atomizers, air inhalation devices and other packaging and equipment known or yet to be developed.

25 “Cold and influenza-like symptoms” refers to symptoms typically associated with respiratory tract viral infections. These symptoms include, but not limited to nasal congestion, chest congestion, sneezing, rhinorrhea, fatigue or malaise, coughing, fever, chills, body ache, sore throat and headache and other known cold and influenza-like symptoms.

30 “Respiratory viruses” refers to those viruses that are causal agents of cold and influenza-like symptoms. These viruses include Rhinovirus, Myxovirus (Influenza virus), Paramyxovirus (Parainfluenza virus), Respiratory Syncytial virus, Adenovirus and Coronavirus.

“Pharmaceutically acceptable vehicle” refers to any solid, liquid or gas combined with compound in the composition of the present invention to deliver the compound to the respiratory tract of the user. These vehicles are generally regarded as safe for use in humans.

DETAILED DISCUSSION OF THE INVENTION

The compositions of the present invention comprise pyroglutamic acid and an organic acid having a pKa value from about 3.0 to about 5.0, wherein the combination of said pyroglutamic and organic acids provides a surface pH of the nasal cavity tissue from about pH 3.5 to 5.5. Upon application to the nasal tissues, the compositions create a hostile environment to viruses. Such an environment deters one from being infected by viruses responsible for the symptoms generally recognized and mentioned above. The present invention also includes treating already infected subjects in order to mitigate the above-mentioned cold and flu symptoms. Also claimed as part of the invention are the methods of reducing or eliminating the possibility of acquisition of such viruses when exposed to high risk of infection in environments including public buildings such as school classrooms and workers' offices.

Pyroglutamic Acid

The nasal compositions of the present invention comprise a safe and effective amount of pyroglutamic acid or PCA. As used herein, pyroglutamic acid collectively refers to its stereoisomers and tautomers. Pyroglutamic acid, which is also referred to as pyrrolidone carboxylic acid has two stereoisomers (D and L) and each are preferred for use herein.

The D stereoisomer of pyroglutamic acid is also known by the following names: D-Proline, 5-oxo- (+)-2-Pyrrolidone-5-carboxylic acid, (+)-Pyroglutamic acid, (R)-2-Pyrrolidone-5-carboxylic acid, 5-Oxo-D-proline, D-2-Pyrrolidone-5-carboxylic acid, D-Pyroglutamic acid, D-Pyrrolidinonecarboxylic acid, and D-Pyrrolidonecarboxylic acid.

The L stereoisomer of pyroglutamic acid is also known by the following names: L-Proline, 5-oxo- (-)-2-Pyrrolidone-5-carboxylic acid, (-)-Pyroglutamic acid, (5S)-2-Oxopyrrolidine-5-carboxylic acid, (S)-(-)-2-Pyrrolidone-5-carboxylic acid, (S)-2-Pyrrolidone-5-carboxylic acid, (S)-5-Oxo-2-pyrrolidinecarboxylic acid, (S)-Pyroglutamic acid, 2-L-Pyrrolidone-5-carboxylic acid, 2-Pyrrolidinone-5-carboxylic acid, 5-Carboxy-2-pyrrolidinone, 5-Oxo-L-proline, 5-Oxoproline, 5-Pyrrolidinone-2-carboxylic acid, Glutimic acid, Glutiminic acid, L-2-Pyrrolidone-5-carboxylic acid, L-5-Carboxy-2-pyrrolidinone, L-5-Oxo-2-pyrrolidinecarboxylic acid, L-5-Oxoproline, L-Glutamic acid, .gamma.-lactam, L-Glutimic acid, L-Glutiminic acid, L-Pyroglutamic acid, L-Pyrrolidinonecarboxylic acid, L-Pyrrolidonecarboxylic acid, Oxoproline, PCA, Pidolic acid, Pyroglutamic acid, Pyrrolidinonecarboxylic acid, Pyrrolidone-5-carboxylic acid, and Pyrrolidonecarboxylic acid.

The DL form of pyroglutamic acid (a mixture of the D and L stereoisomers) is known by the following names: DL-Proline, 5-oxo-(+,-)-2-Pyrrolidone-5-carboxylic acid, (+,-)-Pyroglutamic acid, 5-Oxo-DL-proline, DL-2-Pyrrolidinone-5-carboxylic acid, DL-2-

Pyrrolidone-5-carboxylic acid, DL-Pyroglutamate, DL-Pyroglutamic acid, DL-Pyrrolidonecarboxylic acid, and Oxoproline. The DL form is also commercially available from Ajinomoto under the tradename Ajidew A 100 and Ajidew N 50 (Na-PCA).

Some of the above-listed stereoisomers is commercially available from UCIB, France via
 5 Barnet Products Corp., New Jersey. Such compounds are sold under trade names like Cuivridone (Cu-PCA) and L-FER Pidolate (Fe-PCA), and Pidolidone.

The compositions of the present invention comprise from about 0.01% to about 20% by weight of the composition of pyroglutamic acid, alternatively from about 0.1% to about 10%, from about 0.25% to about 8%, and specifically from about 1% to about 5%.

10 Organic Acids

In addition to PCA, the present invention utilizes organic acids to create a composition hostile to the viruses mentioned above. These organic acids have a dissociation constant (pKa) from about 3.0 to about 5. When combined with PCA, the composition has an increased buffering capacity, providing a surface pH of the tissue treated in the nasal cavities or turbinates
 15 from about 3.5 to about 5.5. These organic acids are at levels from about 0.01% to about 10.00%, alternatively from about 0.05% to about 5.00% and specifically from about 0.10% to about 2.50% of the composition.

Among the organic acids useful in the present invention are selected from the group consisting of ascorbic acid, mono-, di-, tri- carboxylic acids and mixtures thereof. Specific
 20 mono, di or tricarboxylic acids are selected from the group consisting of salicylic, fumaric, benzoic, glutaric, lactic, citric, malonic, acetic, glycolic, malic, adipic, succinic, aspartic, phthalic, tartaric, glutamic, gluconic, and mixtures thereof. Use of such acids is particularly surprising to one skilled in the art in that they create this hostile environment for viruses without significantly irritating the nasal tissues the compositions they contact.

25 Agents are used to adjust the pH of the composition of the present invention to less than 4.5. Therefore, when the composition is applied to nasal tissues, the pH of the composition on the nasal tissues remains from about 3.5 to 5.5, but is not so low as to cause irritation of the nasal tissues. Such pH- adjusting agents include those normally associated with use in topical nasal compositions including sodium bicarbonate, sodium phosphate, sodium hydroxide, ammonium
 30 hydroxide, sodium stannate, triethanolamine, sodium citrate, and combinations thereof. They may be added directly to the composition or formed by interaction within the composition during the pH adjustment process. The pH adjusting agents are generally present in an amount of from about 0.01% to about 5.0% by weight of the composition.

Depending on the desired form and delivery device to be used, compositions of the present invention may include pharmaceutically acceptable vehicles including co-solvents such as ethanol, propylene glycol, glycerol, water-miscible solvent; liquid aerosol propellants and mixtures thereof. Preferably these vehicles are isotonic with human plasma. Preservatives may also be included to prevent microbial contamination of dosing devices or compositions applied to the nose. Such preservatives include those normally associated with topical nasal compositions including benzalkonium chloride, chlorhexidine gluconate, phenyl ethyl alcohol, phenoxyethanol, benzyl alcohol, sorbic acid, benzoic acid, thimerosal, phenylmercuric acetate and combinations thereof.

The vehicle may also contain surfactants to facilitate virus kill as well as aid in spreading the composition throughout the respiratory tract. Gums, mucilages, thickeners, mucoadhesive polymers and mixtures thereof may be included in order to slow the normal physiologic clearance of the solution from the nasal cavity to the oropharynx. Where the composition of the present invention is in the form of a liquid, the combination of ingredients is such that the viscosity of the final composition is less than about 1000 cps at a compositional pH of about 3.5.

Volatile oils, sensates and flavors may also be included to provide desirable in-use smell and taste of the composition. Homoeopathic ingredients may also be included. A detailed, but not necessarily a complete list of such agents is found in The Homoeopathic Pharmacopoeia of the United States, 1999 ed., published by The Pharmacopoeia Convention of the American Institute of Homeopathy, ©1982, Vol. 1-4.

Suitable mucoadhesive polymers useful in the present invention exhibit pH responsiveness. By pH responsiveness, it is meant that upon contacting the mucosal fluids or tissues, the composition becomes sufficiently tacky or viscous to adhere to the tissues and not quickly erode from the surface. This is brought about by a rise in pH when the acidic product comes into contact with the less-acidic mucosal tissues and tissue fluids. This helps maintain the virus-hostile environment for longer on the mucosal surfaces than with a normal fluid product. For example, where the composition is an liquid applied using an atomizing sprayer, upon spraying into the nasal cavity, the composition quickly forms a gel like film that resists erosion due to sneezing, blowing ones nose, or mucociliary clearance.

Mucoadhesive polymers are selected from the group consisting of carboxypolymethylene; carboxyvinyl polymers; homopolymers of acrylic acid crosslinked with an allyl ether of pentaerythritol; homopolymers of acrylic acid crosslinked with an allyl ether of sucrose; homopolymers of acrylic acid crosslinked with divinyl glycol; and mixtures thereof. Homopolymers of acrylic acid crosslinked with an allyl ether of pentaerythritol or an allyl ether

of sucrose are available from B. F. Goodrich Company under the tradename "Carbopol". Specific Carbopols include Carbopol 934, 940, 941, 956, 980 and mixtures thereof. An embodiment of this invention specifically utilizes Carbopol 980. Polymers of this type have slightly acidic carboxyl group substituents. Such polymers generally have a pH of around 3 in water and are generally used by neutralization during preparation of compositions to form viscous gels. Generally these polymers are used from about 0.01% to about 2.5%. Homopolymers of acrylic acid crosslinked with divinyl glycol are available from B. F. Goodrich Company as polycarbophils under the trade name "Noveon." In the present invention the mucoadhesive polymers are used in combination with the acids to form a low viscosity liquid that upon application to mucosal tissue and fluid form gels in situ.

Water may also be present in the composition of the present invention. The water, employed in the present invention should, preferably, be de-ionized and free of organic impurities. Water comprises from about 50% to 99.99%, alternatively from about 80% to about 99.95%, and specifically from about 95% to about 99.9%, by weight of the substance. This amount of water includes the free water that is added plus that amount that is introduced with other materials.

Where the composition of the present invention is a solid form the vehicle may be applied in a powder form without use of a specific vehicle. However, vehicles are often added to aid in processing of the compounds, providing acceptable flowability and a particle size of greater than 10 microns for nasal inhalant application. Other particulate or powdered pharmaceutically acceptable filler materials may be combined with compounds of the present invention to facilitate flowability, stability, handling, hygroscopicity; favorable flavor, taste and, or sensation. In the present invention, the solid vehicle is from 0% to about 99.99%, preferably from about 1% to about 99.9%, alternatively from about 10% to about 99% of the composition.

Chelating Agents

The composition may include chelating agents to enhance antiviral activity by denying the virus metal ions. Not to be bound by theory, it is reasonable to postulate that metal cations play a major role in the formation of oxidizing species. Oxidising reactions and free radical formation can contribute to cellular damage in inflammatory diseases. Chelating agents useful in the present invention include those that chelate transition metal ions such as iron, copper, zinc and other such metals. The chelating agents useful in present invention are stable and effective in non-aqueous and aqueous medium and in pH range between 3 to 5. Specific chelating agents are selected from the group consisting of phytic acid, disodium and calcium salts of ethylene diamine tetraacetic acid (EDTA), tetrasodium EDTA, sodium hexametaphosphate (SHMP),

di(hydroxyethyl)glycine, 8-hydroxyquinoline and mixtures thereof. In the present invention, the chelating agents are used at levels from about 0.001% to 10.00%, alternatively from about 0.005% to about 5.0%, and specifically from about 0.01% to about 2% by weight of the composition.

5 Metal Salts

The nasal compositions of the present invention may comprise a safe and effective amount of a metal salt. Metal ions such as iron, silver, copper and zinc are known to exhibit antiviral properties. Zinc and its possible effects on common colds has been extensively documented, The Handbook for Curing the Common Cold, George A. Eby, published 1994,
 10 George Eby Research, Texas, USA. The mechanism of its action is thought to be multifactorial. Zinc ions have been shown to be both antiviral and antibacterial. They are believed to inhibit cleavage of rhinovirus polypeptides, preventing replication and formation of infective virions. Zinc ions reduce the ability of rhinoviruses to penetrate cell membranes, partly by lowering expression of intercellular adhesion molecule ICAM. Zinc ions have also been shown to
 15 stimulate T-cell lymphocytes, including production of the natural antiviral, interferon-gamma. They stabilize cell plasma membranes, protecting cells from cytotoxic agents, and preventing cell leakage. Metal ions may be in the form of salts or as complexes with anions.

Suitable metal salts include, but are not limited to, salts of metals selected from the groups consisting of Mn, Ag, Zn, Sn, Fe, Cu, Al, Ni, Co and combinations thereof. Preferably,
 20 the metal salts include salts of metals selected from the group consisting of Cu, Fe, Zn, and combinations thereof.

The metal salts include, but are not limited to, physiologically acceptable metal salts selected from the group consisting of salicylates, fumarates, benzoates, glutarates, lactates, citrates, malonates, acetates, glycolates, thiosalicylates, adipates, succinates, gluconates, aspartates, glycines, tartarates,
 25 malates, maleates, ascorbates, chlorides, sulphates, nitrates, phosphates, fluorides, iodides, pidolates and combinations thereof. One embodiment is where the metal salts are selected from the group consisting of acetates, ascorbates, chlorides, benzoates, citrates, gluconates, glutarates, lactates, malates, malonates, salicylates, succinates and combinations thereof. Another alternative is wherein the metal salts are selected from the group consisting of zinc acetate, zinc chloride, zinc ascorbate, zinc gluconate, zinc
 30 pidolate and combinations thereof. Specifically the metal salt including is selected from the group consisting of acetic acid, ascorbic acid, citric acid, gluconic acid, pyroglutamic acid, glutaric acid, salicylic acid salts or metal complexes of zinc, copper, tin, silver, iron, and mixtures thereof.

Without being limited by theory, it is believed that in the compositions of the present invention, the pyroglutamic acid and metal salt complex to form a metal-acid complex that have been found to provide a synergistic immediate and residual anti-viral efficacy.

- In the compositions of the present invention, the metal salt is present in amount such that
- 5 the metal salt comprises from about 0.001% to about 20%, by weight of the composition, alternatively from about 0.01% to about 10%, from about 0.05% to about 5%, and specifically from about 0.05% to about 2%. Alternatively, the pyroglutamic acid and metal salt may be complexed prior to making the compositions of the present invention thereby forming a pyroglutamic acid-metal complex. In this instance, the complex is preferably present in an
- 10 amount of from about 0.001% to about 20%, by weight of the composition, alternatively from about 0.01% to about 10%, and specifically from about 0.1% to about 5%.

EXAMPLES

The following are non-limiting examples of compositions of the present invention. All ingredients are by weight of 100 grams of the composition:

15 Example 1:

Component	% (w/w)
PCA (Pyroglutamic Acid)	1.00
Ascorbic Acid	1.00
Phytic Acid	1.00
Mucoadhesive Polymer ¹	1.00
Eucalyptol	0.01
Phenyl Ethyl Alcohol	0.50
Water	QS

1. Carbopol 980 available from available from B. F. Goodrich Company

Manufacturing Directions:

- Disperse the Carbopol in chilled water. Add and dissolve the acidic ingredients with stirring. Premix the eucalyptol in the phenyl ethyl alcohol and add and dissolve with stirring. Adjust the
- 20 pH to 3.5 with addition of sodium hydroxide.

Fill dropper vials with the solution and cap. Spray 100 microlitres of the solution into each nostril or each nostril or turbinate. Repeat three times daily.

Example II:

Component	% (w/w)
PCA (Pyroglutamic Acid)	1.00

Ascorbic Acid	1.00
Zinc Acetate	0.33
Mucoadhesive Polymer ¹	1.00
Eucalyptol	0.01
Water	QS

1. Carbopol 980 available from available from B. F. Goodrich Company

Manufacturing Directions:

Disperse the Carbopol in chilled water. Add and dissolve the acidic ingredients and the zinc acetate with stirring. Premix the eucalyptol in the phenyl ethyl alcohol and add and dissolve with stirring. Adjust the pH to 3.5 with addition of sodium hydroxide.

Fill dropper vials with the solution and cap. Spray 100 microlitres of the solution into each nostril and turbinate. Repeat three times daily.

Example III:

Component	% (w/w)
PCA (Pyroglutamic Acid)	1.00
Citric Acid	0.50
Phytic Acid	1.00
Mucoadhesive Polymer ¹	1.00
Eucalyptol	0.01
Phenyl Ethyl Alcohol	0.50
Water	QS

1. Carbopol 980 available from available from B. F. Goodrich Company

10 **Manufacturing Directions:**

Disperse the Carbopol in chilled water. Add and dissolve the acidic ingredients with stirring. Premix the eucalyptol in the phenyl ethyl alcohol and add and dissolve with stirring. Adjust the pH to 3.5 with addition of sodium hydroxide.

Fill dropper vials with the solution and cap. Spray 100 microlitres of the solution into each nostril or turbinate. Repeat three times daily.

Example IV:

Component	% (w/w)
PCA (Pyroglutamic Acid)	1.00
Citric Acid	0.50
Zinc Acetate	0.33

Mucoadhesive Polymer ¹	1.00
Eucalyptol	0.01
Phenyl Ethyl Alcohol	0.50
Water	QS

1. Carbopol 980 available from available from B. F. Goodrich Company

Manufacturing Directions:

- Disperse the Carbopol in chilled water. Add and dissolve the acidic ingredients and the zinc acetate with stirring. Premix the eucalyptol in the phenyl ethyl alcohol and add and dissolve with stirring. Adjust the pH to 3.5 with addition of sodium hydroxide.

Fill dropper vials with the solution and cap. Spray 100 microlitres of the solution into each nostril or turbinate. Repeat three times daily.

Example V

Component	% (w/w)
PCA (Pyroglutamic Acid)	1.00
Sodium Citrate	0.75
Eucalyptol	0.010
Ethanol	1.00
Lactose Powder	QS to 100%

Manufacturing Directions:

- Blend the PCA and Sodium citrate together in a V-mixer to form a homogenous mix. Micronise the mixture in a fluid energy mill. Blend the micronised material by geometric addition with the lactose. Dissolve the eucalyptol in in ethanol and spray coat the powder. Evaporate the ethanol by pan drying. Blend the PCA.

- Fill dry powder nasal inhalation metering pumps with the powder. Apply 10 milligrams of the powder to each nostril or turbinate.

Example VI

Component	% (w/w)
PCA (Pyroglutamic Acid)	1.00
Sodium Citrate	0.75
Sorbitan Trioleate	0.40
Propellants ¹	97.85

1. Dupont Propellants 114 and 12 (1:1)

Manufacturing Directions:

Blend the PCA and sodium citrate together in a V-mixer to form a homogenous mix. Micronise the mixture in a fluid energy mill. Dissolve the sorbitan trioleate in the mixed propellants. Disperse the PCA/Sodium citrate blend in the sorbitan trioleate/ propellant liquid. Fill the suspension into pressurized metered dose inhalers using standard filling techniques.

- 5 Administer 100 microlitres from the metered dose inhaler into each nostril or turbinate.

What is claimed is:

1. A low irritation nasal composition for prevention and treatment of cold and influenza viruses comprising pyroglutamic acid and an organic acid having a dissociation constant (pKa) value from about 3.0 to about 5.0 wherein the combination of said pyroglutamic and organic acids provides a surface pH of the nasal cavity tissue from about 3.5 to about 5.5.
2. The composition according to claim 1 wherein the pyroglutamic acid is at a level from about 0.01% to about 20% of the composition.
3. The composition according to claim 1 comprising from about 0.01% to about 10.00% of an organic acid.
4. The composition according to claim 3 wherein the organic acid is selected from the group consisting of ascorbic acid, mono-, di-, tri- carboxylic acids and mixtures thereof.
5. The composition according to claim 4 wherein the organic acid is selected from the group consisting of salicylic, fumaric, benzoic, glutaric, lactic, citric, malonic, acetic, glycolic, malic, adipic, succinic, aspartic, phthalic, tartaric, glutamic, gluconic, and mixtures thereof.
6. The composition according to claim 1 comprising a mucoadhesive agent wherein the viscosity of the final composition is less than about 1000 cps wherein the composition has a pH of about 3.5.
7. The composition according to claim 5 wherein the mucoadhesive agent is selected from the group consisting of carboxypolymethylene; carboxyvinyl polymers; homopolymers of acrylic acid crosslinked with an allyl ether of pentaerythritol; homopolymers of acrylic acid crosslinked with an allyl ether of sucrose; homopolymers of acrylic acid crosslinked with divinyl glycol; and mixtures thereof.
8. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 1.
9. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 5.
10. The composition according to claim 1 comprising a chelating agent.

11. The composition according to claim 10 wherein the chelating agent is at a level from about 0.01% to about 10% of the composition.
12. The composition according to claim 11 wherein the chelating agent is selected from the group consisting of phytic acid, disodium and calcium salts of ethylene diamine tetraacetic acid (EDTA), tetrasodium EDTA, sodium hexametaphosphate (SHMP), di(hydroxyethyl)glycine, 8-hydroxy-quinoline and mixtures thereof.
13. The composition according to claim 10 comprising a mucoadhesive agent wherein the viscosity of the final composition at a pH of 3.5 is less than about 1000 cps.
14. The composition according to claim 13 wherein the mucoadhesive agent is selected from the group consisting of carboxypolymethylene; carboxyvinyl polymers; homopolymers of acrylic acid crosslinked with an allyl ether of pentaerythritol; homopolymers of acrylic acid crosslinked with an allyl ether of sucrose; homopolymers of acrylic acid crosslinked with divinyl glycol; and mixtures thereof.
15. The composition according to claim 14 wherein the organic acid comprises from about 0.01% to about 10% of the composition.
16. The composition according to claim 15 wherein the organic acid is selected from the group consisting of ascorbic acid, mono-, di-, tri- carboxylic acids and mixtures thereof.
17. The composition according to claim 16 wherein the organic acid is selected from the group consisting of salicylic, fumaric, benzoic, glutaric, lactic, citric, malonic, acetic, glycolic, malic, adipic, succinic, aspartic, phthalic, tartaric, glutamic, gluconic, and mixtures thereof.
18. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 10.
19. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 13.
20. The composition according to claim 1 comprising metal salts.

21. The compositions according to claim 20 wherein the metal salt is at a level from about 0.01% to about 10% of the composition.
22. The compositions according to claim 21 wherein the metal salt is selected from the group consisting of acetates, ascorbates, chlorides, benzoates, citrates, gluconates, glutarates, lactates, malates, malonates, salicylates, succinates and combinations thereof.
23. The composition according to claim 22 wherein the organic acid comprises from about 0.01% to about 10% of the composition.
24. The composition according to claim 23 wherein the organic acid is selected from the group consisting of ascorbic acid, mono-, di- and tri- carboxylic acids and mixtures thereof.
25. The composition according to claim 24 wherein the organic acid is selected from the group consisting of salicylic, fumaric, benzoic, glutaric, lactic, citric, malonic, acetic, glycolic, malic, adipic, succinic, aspartic, phthalic, tartaric, glutamic, gluconic, and mixtures thereof.
26. The composition according to claim 20 comprising a mucoadhesive agent wherein the viscosity of the final composition is less than about 1000 cps wherein the composition has a pH of about 3.5.
27. The composition according to claim 26 wherein the mucoadhesive agent is selected from the group consisting of carboxypolymethylene; carboxyvinyl polymers; homopolymers of acrylic acid crosslinked with an allyl ether of pentaerythritol; homopolymers of acrylic acid crosslinked with an allyl ether of sucrose; homopolymers of acrylic acid crosslinked with divinyl glycol; and mixtures thereof.
28. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 20.
29. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 23.
30. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 26.

31. The composition according to claim 10 comprising a metal salt.
32. The compositions according to claim 31 wherein the metal salt is from about 0.001% to about 20% of the composition.
33. The compositions according to claim 32 wherein the metal salt are selected from the group consisting of acetates, ascorbates, chlorides, benzoates, citrates, gluconates, glutarates, lactates, malates, malonates, salicylates, succinates and combinations thereof.
34. The composition according to claim 31 wherein the chelating agent is at a level from about 0.01% to about 10% of the composition.
35. The composition according to claim 34 wherein the chelating agent is selected from the group consisting of phytic acid, disodium and calcium salts of ethylene diamine tetraacetic acid (EDTA), tetrasodium EDTA, sodium hexametaphosphate (SHMP), di(hydroxyethyl)glycine, 8-hydroxyquinoline and mixtures thereof.
36. The composition according to claim 31 comprising a mucoadhesive agent wherein the viscosity of the final composition is less than about 1000 cps wherein the composition has a pH of about 3.5.
37. The composition according to claim 36 wherein the mucoadhesive agent is selected from the group consisting of carboxypolymethylene; carboxyvinyl polymers; homopolymers of acrylic acid crosslinked with an allyl ether of pentaerythritol; homopolymers of acrylic acid crosslinked with an allyl ether of sucrose; homopolymers of acrylic acid crosslinked with divinyl glycol; and mixtures thereof.
38. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 31.
39. A low irritation nasal composition for prevention and treatment of influenza viruses comprising an organic acid having a dissociation constant (pKa) value from about 3.0 to about 5.0 and pH less than about 4 and a buffering capacity to provide a surface pH of the nasal cavity tissue from about pH 3.5 to about 5.5

40. The composition according to claim 39 comprising from about 0.01% to about 10% of the organic acid.
41. The composition according to claim 40 wherein the organic acid is selected from the group consisting of ascorbic acid, mono-, di-, tri- carboxylic acids and mixtures thereof.
42. The composition according to claim 41 wherein the organic acid is selected from the group consisting of salicylic, fumaric, benzoic, glutaric, lactic, citric, malonic, acetic, glycolic, malic, adipic, succinic, aspartic, phthalic, tartaric, glutamic, gluconic, and mixtures thereof.
43. The composition according to claim 39 comprising a mucoadhesive agent wherein the viscosity of the final composition is less than about 1000 cps wherein the composition has a pH of about 3.5.
44. The composition according to claim 43 wherein wherein the mucoadhesive agent is selected from the group consisting of carboxypolymethylene; carboxyvinyl polymers; homopolymers of acrylic acid crosslinked with an allyl ether of pentaerythritol; homopolymers of acrylic acid crosslinked with an allyl ether of sucrose; homopolymers of acrylic acid crosslinked with divinyl glycol; and mixtures thereof.
45. The composition according to claim 39 comprising a chelating agent.
46. The composition according to claim 45 wherein the chelating agent is at a level from about 0.01% to about 10.00% of the composition.
47. The composition according to claim 46 wherein the chelating agent is selected from the group consisting of phytic acid, disodium and calcium salts of ethylene diamine tetraacetic acid (EDTA), tetrasodium EDTA, sodium hexametaphosphate (SHMP), di(hydroxyethyl)glycine, 8-hydroxyquinoline and mixtures thereof.
48. The composition according to claim 39 comprising metal salts.
49. The compositions according to claim 48 wherein the metal salts are at a level from about 0.001% to about 20% of the composition.

50. The compositions according to claim 49 wherein the metal salts are selected from the group consisting of acetates, ascorbates, chlorides, benzoates, citrates, gluconates, glutarates, lactates, malates, malonates, salicylates, succinates and combinations thereof.
51. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 39.
52. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 45.
53. A method for preventing and treating cold and influenza viruses wherein the method comprises the step of spraying into the nasal turbinates the composition according to claim 48.

ABSTRACT
COMPOSITIONS FOR PREVENTION AND TREATMENT
OF COLD AND INFLUENZA-LIKE SYMPTOMS
AND THEIR METHODS OF USE

The present invention is for compositions and their methods for prevention and treatment of cold and influenza-like symptoms due to respiratory tract viral infections. These compounds and their method of application are effective in both preventing the onset of the symptoms of colds and influenza or significantly mitigating them if already afflicted with such symptoms.

DECLARATION COMBINED WITH POWER OF ATTORNEY

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Attorney Docket No. 8308

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled COMPOSITIONS FOR PREVENTION AND TREATMENT OF COLD AND INFLUENZA-LIKE SYMPTOMS AND THEIR METHODS OF USE the specification of which

(check one) ☒ is attached hereto.
☐ was filed on _____ as United States Application No. or
PCT International Application Serial No. _____
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations §1.56.

I hereby claim foreign priority benefits under Title 35 United States Code §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)Priority Claimed

(Number)	(Country)	(Day/Month/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

Application Serial No.	Filing Date	Application Serial No.	Filing Date

I hereby claim the benefit under Title 35 United States Code §120 of any United States application(s), or §365(c) of any PCT International application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35 United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (If applicable)
09/421,131		10/19/1999	

As named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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